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March 19, 1998

Dr. C.W. Jameson
National Institute of Environmental Health Sciences
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Research Triangle Park, NC 27709

Dear Dr. Jameson,

The Electric Power Research Institute (EPRI) is submitting technical comments concerning the proposed listing by the National Toxicology Program of nickel and nickel compounds in the category of substances "Known to be a Human Carcinogen" (Federal Register, February 3, 1998, Volume 63, Number 22, pp. 5565-5567). The attached comments reflect a review of relevant experimental and epidemiological information on the carcinogenicity of nickel and nickel compounds, substantially performed by Dr. Annette Shipp of ICF Kaiser Engineers under EPRI sponsorship.

If there are any questions, I can be reached at (650) 855-7929 [fax: (650) 855-1069; e-mail: llevin@epri.com].

Sincerely,

Leonard Levin

Leonard Levin, Ph.D.
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LL:hoh

Enclosure

Comments by
Electric Power Research Institute
to National Toxicology Program
Concerning Proposed Listing of
Nickel and Nickel Compounds as Human Carcinogens

March 19, 1998

The National Toxicology Program issued a notice in the Federal Register dated February 3, 1998, proposing to list "nickel and nickel compounds" as "Known to be a Human Carcinogen." The Electric Power Research Institute is submitting the comments below in response to that notice.

Introduction

The USEPA has developed inhalation unit risk factors for nickel refinery dust and nickel subsulfide based on the results of four epidemiological studies in which workers were exposed to nickel refinery dust (Chovil et al. 1981, Enterline and Marsh 1982, Magnus et al. 1982, Peto et al. 1983). The USEPA has not developed inhalation unit risk factors for other nickel compounds, but based on the results of animal studies (as noted in IRIS), the USEPA has classified nickel carbonyl as a probable human carcinogen (B2). However, the USEPA noted that quantitative estimates of carcinogenic risks from inhalation exposures to nickel carbonyl were not possible due to poor survival in control and treated animals in one study and an inappropriate route of exposure (intravenous) in another study. IARC has recently classified nickel compounds, including soluble nickel, as human carcinogens. The validity of this classification, and the proposed classification by NTP, is discussed below.

Overview of Toxicity Studies

Several epidemiological studies have been conducted in which mortality rates due to various causes were examined in workers exposed to nickel, usually in the form of nickel refinery dust, via inhalation for durations of from less than 1 year to many years (Enterline and Marsh 1982; Doll et al. 1977; Chovil et al. 1981; Magnus et al. 1982; Peto et al. 1983; Bernacki et al. 1978; Polednack 1981; Cox et al. 1981; Cragle et al. 1984; Andersen et al. 1996). Specific information with regard to the nickel species to which workers may have been exposed was not provided in all studies; however, most of the work involved nickel refinery dust, which has been estimated to contain approximately 50% nickel subsulfide (USEPA 1995a). In some of the studies, the authors speculated as to the nickel species that may have been present based on materials and processes used in the plants (Bernacki et al. 1978; Chovil et al. 1981; Andersen et al. 1996), while in other studies, more specific information was given (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh

1982; Polednak 1981). In most of the studies, mortality rates, due to various types of cancer observed in nickel-exposed workers, were compared to the expected mortality rates observed in the general population and/or with other worker groups. With the exception of Magnus et al. (1982) and Andersen et al. (1996), the smoking habits of the workers, which would be expected to have an impact on lung tumor incidence, were not considered.

With the exception of the results reported by Andersen et al. (1996), the results from occupational cohorts exposed to nickel refinery dust are consistent in that increased mortality ratios due to lung or sinus cancer were reported in workers exposed to high concentrations of nickel refinery dust (Enterline and Marsh 1982, Doll et al. 1977, Chovil et al. 1981, Magnus et al. 1982, Peto et al. 1983), which is composed of approximately 50% nickel subsulfide (USEPA 1995a). A positive association between nickel refinery dust exposure and lung/or nasal sinus cancers was predominantly found in workers employed (1) in high exposure areas; (2) for longer durations; and (3) during years in which exposure was most likely less controlled, i.e., during the early years of plant operations.

In other epidemiological studies (Bernacki et al. 1978; Polednak 1981; Cragle et al. 1984; Cox et al. 1981), there were no increases in deaths due to lung or nasal sinus cancer in workers exposed to nickel oxides, nickel sulfate, nickel chloride, or nickel powder. The negative results reported in Bernacki et al. (1978), Polednak (1981), and Cox et al. (1981) may have been the result of differences in the level and duration of exposure to different nickel species. Another and perhaps a more plausible explanation is that the workers in these apparently negative studies were not exposed to nickel subsulfide.

The results reported by Andersen et al. (1996) differ from those reported in other studies. Andersen et al. (1996) reported that increases in deaths due to lung cancer were associated with exposures to soluble nickel compounds, either alone or in combination with other nickel compounds. Soluble nickel compounds were defined as nickel sulfate, nickel chloride, nickel carbonate, and nickel hydroxide. However, the analyses conducted by Andersen and colleagues relied on a key assumption, due to limited air sampling data (air samples were collected intermittently for total nickel only). Air concentrations of specific nickel species were assumed to have been present in the same proportions as in the material being handled by those in the various job categories. This could potentially lead to over- or underestimation of exposures to different nickel species, i.e., exposures to insoluble nickel species such as nickel subsulfide could be estimated incorrectly. The effects of such potential errors are unknown; if the statistical association between the soluble and insoluble nickel species were presented, a better understanding of the potential consequences of measurement error would be possible.

Andersen et al. (1996) employed a multivariate linear regression analysis to determine the associations among soluble nickel, insoluble nickel, and deaths due to lung cancer. In the regression model, smoking habits via use of a bivariate variable (ever/never smoked) and age were considered; however, the only insoluble form of nickel considered was nickel oxide; the possible interaction or confounding between other insoluble nickel species (e.g., nickel subsulfide) and soluble nickel species was not considered. As the study authors noted it was virtually impossible to identify a population of workers that would be exposed exclusively to either soluble or insoluble nickel due to the complexity of the nickel refining process. Therefore, concurrent exposures to other insoluble nickel compounds, such as nickel subsulfide, cannot be discounted, and the increases in deaths due to lung cancer may or may not be solely attributable to exposures to soluble nickel.

Table 6 in the Andersen et al. (1996) paper indicates that all excess lung cancers attributed to nickel exposure are among the smoking population, the relative risk increasing from 2.9 to 5.1 with nickel exposure among those who ever smoked. The relative risk associated with total nickel exposure among those who never smoked was 1.1 (not statistically significant). The authors interpret this result to be an indication of an interaction effect between smoking and nickel exposure. The result could also reflect the use of a bivariate smoking variable rather than a variable representing the relative amount of cigarettes smoked. If the latter changed over time or differed by job classification, it would also have influenced the results. This very issue is addressed by Brenner (1997), who shows "that, under certain conditions, control for crudely classified covariates can even be worse than not controlling for such covariates at all." The results of animal inhalation studies support the results of the epidemiological studies and provide further evidence that there is a distinct difference in potency among nickel compounds. For example, the results of animal studies with nickel subsulfide suggest that inhalation exposure to nickel subsulfide may result in an increased incidence of lung tumors in rats (Ottolenghi et al. 1975; NTP 1996a; Dunnick et al. 1995). However, dose-related increases in the incidence of lung tumors were not reported in animals following inhalation exposure to nickel oxide (Horie et al. 1985, Takenaka et al. 1985, Wehner et al. 1975; NTP 1996b; Dunnick et al. 1995), nickel carbonyl (Sunderman and Donnelly 1965) or nickel sulfate hexahydrate (NTP 1996c; Dunnick et al. 1995), suggesting that not all nickel compounds are equally carcinogenic in animals following inhalation exposure.

The differences in kinetics, i.e., clearance from the lung and delivery to the target tissues, are likely to be at least partially responsible for the differences in potency among nickel compounds (Oller et al. 1997). For example, the more soluble nickel compounds, such as nickel sulfate, are cleared from the lung more quickly, thus decreasing the dose that is delivered to the target tissue. In contrast, the more insoluble nickel compounds, such as nickel subsulfide or

nickel oxide, are cleared more slowly from the lung. With continued exposures to high levels, lung clearance mechanisms may be overwhelmed and a larger dose delivered to the target tissue. Thus, the potential for more nickel to be taken into the cell is increased.

Another factor in the differences in potency between nickel compounds is the difference in uptake of the different nickel compounds by the cell. Certain forms of nickel, such as nickel subsulfide, are preferentially taken up by the cell by endocytosis, when compared to the uptake of other forms of nickel (Costa and Heck 1982; Costa et al. 1981). Once in the cell, nickel is transported to the nucleus where it may produce carcinogenic effects by altering gene expression, by binding with heterochromatin resulting in damage or deletion of senescence or tumor suppressor genes, or by producing oxygen free radicals by a Ni^{3+} to Ni^{2+}–type mechanism (Sen and Costa 1986; Lee et al. 1995; Huang et al. 1994; Costa et al. 1992, 1994; Conway and Costa 1989; Oller et al. 1997). The free radicals could then bind to DNA, producing nonspecific DNA damage. Other forms of nickel, however, are not taken up as readily by the cells (Costa and Heck 1982), and, as a result, are not delivered to the nucleus. Therefore, carcinogenic effects would not be expected to be manifested.

To summarize:

- Several epidemiological studies have evaluated the potential associations between nickel and lung cancer, as well as nickel and other forms of cancer, in workers occupationally exposed to nickel, usually occurring as nickel refinery dust. The most recent such study, which concludes there is evidence of excess mortality due to exposure to forms of soluble nickel, has a number of unresolved questions associated with it. These questions do not allow strong conclusions to be drawn about the study outcome.

- The potential carcinogenicity of nickel–containing compounds has also been evaluated in animal studies. The results of these studies have suggested that, following inhalation exposure, certain forms of nickel, specifically nickel subsulfide (a major constituent of nickel refinery dust) may result in an increased incidence of nasal sinus or lung cancer in animals and humans. However, based on the epidemiological evidence and the results of the animal studies, inhalation exposures to the more soluble forms of nickel alone have generally not been associated with increases in the incidence of tumors. This suggests a major difference in the carcinogenic potency between the relatively insoluble nickel compounds, such as nickel subsulfide, and the soluble nickel compounds.

- One possible reason for the differences in potency between nickel compounds is differences in clearance from the lung. The insoluble nickel compounds are cleared more slowly, eventually overwhelming clearance

mechanisms, such as alveolar macrophages. The end result is that a larger dose is delivered to the target tissues.

- A second factor responsible for differences in potency is differences in uptake of nickel by the cell. For example, nickel subsulfide is taken up by the cell more readily than other forms of nickel, and once inside the cell would be free to exert any carcinogenic effects. However, if cell uptake of nickel does not occur then carcinogenic effects would not be expected.

Therefore, based on the results of the epidemiological studies and the animal toxicity studies as well as the differences in clearance and cell uptake among nickel compounds, classification of all nickel compounds (soluble and insoluble) as carcinogenic is not supported by the evidence.

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